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CfDNA testing for diagnosis of sickle cell disease: meta-analysis

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Objective

Sickle cell disease (SCD) is an autosomal recessive blood disorder, caused by a single base-pair mutation in the β globin gene (HBB). Approximately 300.000 children are born every year with the disease globally. According to current NHS national population screening programme, a screening by a blood test is offered to all pregnant women living in areas with high prevalence of SCD. The objective of the present programme is to ensure that screening tests are offered by 8–10 weeks of pregnancy, so that early prenatal diagnosis can be offered. The challenge is that 36% of the time the father's sickle status is not known and invasive diagnosis has a risk of miscarriage The use of cf DNA test or non invasive prenatal testing (NIPT) for the detection of fetuses with sickle-cell anemia (SCA) could provide a solution. Different approaches have been described in the literature, including the exploitation of imbalance in relative haplotype dosage (RHDO) and the use of Relative Mutation Dosage(RMD). The former approach is assessing the dosage of numerous mutation or WT allele-linked single nucleotide polymorphisms (SNPs) to report which haplotypes are established to be overrepresented and thus, have been inherited by the fetus. On the other hand, in the RMD approach, the relative abundance of the WT and mutant alleles themselves is used to infer the fetal genotype. The main aim of this systematic review and meta-analysis is to study the sensitivity and specificity of NIPD as a diagnostic tool for sickle cell disease, and to propose amendments to the current screening pathway, which would involve NIPD as a substitution of invasive prenatal diagnosis (PND).

Methods

The eligible studies assessed the sensitivity and specificity as well as positive and negative predictive values for sickle cell disease using NIPT. In the studies that were included, there have to be more than 2 subjects, high sensitivity and sensitivity, of 100% respectively, an index non-invasive test with a control group and a verification of their results, by the gold standard (e. g. amniocentesis or chorionic villus sampling). As compared with the 2016 version of this systematic review and meta-analysis, individual patient data was sought for all included studies. Inclusion of trials was not restricted by language, publication date or country. Systematic reviews and observational studies were excluded. We have screened the relevant papers published in the literature from 1996 to date using Rayyan. Two trials met the inclusion criteria. Both studies were performed in the United Kingdom in 2019 and 2020 respectively. The pooled studies included a total of 121 participants. Both papers, included the non-invasive pre-natal testing of pregnant females, whose fetuses have the potential to be sickle cell disease patients or carry the sickle cell trait (either mother or father are sickle cell disease carriers or are themselves sickle cell patients). In the first study group by Cutts et al. , the participants were noted to be 8 to 17 weeks pregnant, whereas in the second group by Van Campen et al. , were 8 to 35 weeks of gestation. Out of 2 studies, the sensitivity and specifity were recorded, as well as the following parameters were examined; target alleles, gestational age, fetal fraction, sample volume, sample type, method of DNA extraction and method of PCR.

Results

In the current literature, there is a small number of studies that have investigated the sensitivity and specificity of NIPT for the diagnosis of fetuses with a potential risk of having sickle cell anemia disease. Cutts et al. , have showed that the NIPT demonstrates 100% sensitivity and NPV for fetal fractions 0.5% and 100% specificity and PPV for fetal fractions 4%. Similarly, the study by Van Campen et al. , has showed that MPS-based SCD NIPD assay has a 100% clinical sensitivity and specificity, using a single molecular genetic testing platform. Similarly, it was highlighted that a fetal fraction >4% is required. The results of our meta-analysis show that the NIPT can be used as a non-invasive screening tool in any clinical scenario in which the exclusion of SCA or any other recessive disorder is important. In this method, the knowledge of paternal genotype was not needed, which allows a straightforward adaptation to the antenatal routine screening, with an excessive turnaround time.

Conclusion

This review reveals that the NIPT could be used as a reliable screening test for the detection of babies that potentially have sickle cell disease. It becomes apparent that this method could be used in countries with high prevalence of SCD, where the access to the invasive prenatal testing is difficult due to its high cost and low number of doctors trained to perform such procedures. Lastly, similar test could be adapted and used for the diagnosis and detection of dominant monogenetic disorders, autosomal recessive conditions and in novo mutations. Further validation studies should be carried out to confirm the clinical utility and diagnostic accuracy.